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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,858	12/05/2001	David C. Yeomans	582.02	8925

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EXAMINER	
SHARAREH, SHAHNAM J	
ART UNIT	PAPER NUMBER
1617	7

DATE MAILED: 10/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/006,858	YEOMANS, DAVID C.	
	Examiner	Art Unit	
	Shahnam Sharareh	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5-6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-13 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating discogenic pain by administering capsaicin or resiniferatoxin ("RTX"), does not reasonably provide enablement for methods of treating any type of pain by administering any Vanilloid Receptor 1 ("VR1") agonist. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention provides for methods of treating any type of pain, such as headache or earache or pain associated with wounds, by administering any VR1 agonist.

(2) The state of the prior art

The use of VR1 agonist such as capasaicin and RXT to treat arthritic pain or pain secondary to shingles is well established. However, the art seems to lack a teaching for treating all types of pain by administering any VR 1 agonist. The art does not provide adequate guidelines for identifying VR1 agonists that are effective against pains caused by headaches, ear or eye aches or even pain secondary to skin injuries and wounds. In fact, there is no unified common core among all types of VR1 agonists that associates such compounds with treatment of all types of pain.

(3) The relative skill of those in the art

The art concerns using vanilloid receptors for pain control utilizing intravertebral routes of administration. Accordingly, the relative skill of those in the art to practice such invention is viewed to include artisans with a sophisticated understanding of pharmacology, pharmaceutical science and surgical science. see MPEP 2164.05(b).

(4) The predictability or unpredictability of the art

The nature of the pharmacological and surgical therapeutics is unpredictable, because there exists substantial interpatient and interspecies variability. For at least pharmacological therapy, attention is drawn to attached Pharmacotherapy, A Pathophysiologic Approach, 2nd ed. Bauer at page 15, 1st para, which states "clinicians should never assume that a serum concentration within the therapeutic range will be safe and effective for every patient." Thus, the nature of the art of therapeutic medicine, in particular pharmacological therapeutics, is unpredictable.

Furthermore, there is no predictability in the art that all VR1 agonists will provide the same clinical endpoint instantly claimed. In fact, the specification does not set forth adequate teaching showing that capsaicin and RXt represent the entire class of the VR1 agonists.

(5) The breadth of the claims

The instant claims encompass methods of treating any pain by any VR1 receptor agonist. First, the breadth of the claims is not limited to discogenic or arthritic pain. Rather, it encompass pains associated with bacterial infection, stress or fatigue. Causes of pain differ in source and etiology. For example, a post surgical pain is

etiologically different from neuralgic pain or from pain secondary to a wound or a trauma.

Second, the breadth of the claims encompass the use of all types of VR1 agonists including, for example, various capsaicin receptor polypeptide such those taught in US Patent 6,335,180. Such polypeptides do not share any chemical characteristics with capsaicin and RTX. Thus, capsaicin and RTX do not represent the entire class of such agonists.

(6) The amount of direction or guidance presented

The specification discloses methods of treating pain in rats using capsacin. No other types VR1 agonists have been exemplified. Neither does specification provide such therapeutic drugs that can satisfy the outcome for the entire scope of the pending claims. Specification provides no guidance as to methods for identifying all VR1 agonists encompass by the scope of the pending claims and treating all types of pain having etiologically different causes.

The amount of guidance provided here merely amounts to a functional relationship between the vanilloid receptor agonist and the cause of pain. Specification merely provide for a compound defined by reference to a desirable characteristic or property. There is not guidance as to which agonist treat which type of pain. Therefore, the teaching of the specification is merely viewed to be an invitation to experimentation

(7) The presence or absence of working examples

A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will possess the alleged activity. See *In re Riat et al.* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr et al.* (CCPA 1971) 444 F 2d 349, 151 USPQ 724. The instant specification at most only provides examples of methods for treating pain with capsaicin. No examples have been set forth describing treatment of all types of pain intravertebrally by any VR1 agonist.

(8) The quantity of experimentation necessary

Considering the above mentioned factors and the fact that there is significance inter-individual variability in using a therapeutic agent, there is extensive variability between the claimed clinical endpoint and the claimed vanilloid agonists. Further, the entire class of VR1 agonist encompass a large group having differences in the mode of action. Thus, one of ordinary skill in the art would be burdened with undue "experimentation study" to determine all the possible types of VR1agonists that can treat any pain intravertebrally. Further, since the nature of therapeutic art is unpredictable as argued above, the entire scope of treating all types of pain using all types of VR1 agonist is not enabled. Accordingly, claims 1-9 are rejected for undue experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

2. Claims 1, 3, 5-6 are rejected under 35 U.S.C. 102(b) as being anticipated Szabo et al (Brain Research 840, 02-98, 1999, IDS, Paper # 6).

The instant claims are directed to method of treating pain comprising administering sufficient amount a VR 1 agonist into the intravertbral space. Administering into interavertebral space is defined in page 10, line 16 of the specification and encompass such routes of administration as intrathecal and intraganglionic administration.

Szabo discloses methods of providing prolong regional analgesia to pain in rats comprising injecting RTX, a VR1 agonist, directly and intrathecally through an epidural catheter. (see abstract; page 92, 3rd para.; page 93, 2nd col. 3rd para.). Szabo describes desensitization of neurons by administering doses of 1, 3, 10, 30, 100 µg/kg which amounts to a dosing range of 200 nanogram to 20 µg in 200 g rats. (see page 93, under

the heading Materials and Methods, 1st para and 5th para). Accordingly, Szabo anticipates the limitations of the instant claims.

Claims 1, 3-6, 8-13 are rejected under 35 U.S.C. 102(e) as being anticipated by Iadarola et al WO 02/076444 A1 ("Iadorola").

Iodorola is a competent prior art under 35 USC 102(e), because it is an international WIPO publication designating United States and was filed in English after Nov. 29, 2000.

Iodorola discloses a rat animal mode for treating chronic pain by ablating VR1 agonists sensitive neurons comprising administering capsacin and RTX in an amount ranging from about 50 nanograms to about 50 micrograms intrathecally or intraganglionically. (see pages 13, line 25-page 14, line 34; page 21-22, examples 3-4; page 23, claims 1-11). Iodorola further discloses the use of local anesthetic such as lidocaine or bupivacaine in combination with capsaicin (see page 15, line 30-page 16, line 2). Iodorola also teaches the pharmaceutical kits comprising a VR1 agonist, a local anesthetic and instruction material describing the use of the kit. (see page 16, lines 12-20; claims 23-27). Therefore, Iodorola anticipates all limitations of the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iodorola in view of Yuzuru Takashai et al ("Takashai") (Neuroscience Letters, 161, 1-3 (1999), IDS, Paper no. 6).

The teachings of Iodorola are described above. Iodorola teaches the use of VR1 agonists to ablate C-fiber neuron. (page 5, lines 13-15; page 11, lines 16-19). Iodorola teaches that his methods can be used in treating pain effecting spinal column. (page 4, line 30-31). Iodorola further teaches his methods to be practiced in human or other mammals (page 16, lines 8-10). Iodorola meets all the limitations of the instant claims, except he does not explicitly treat patients suffering from discogenic pain, nor dose he teach administration of a VR1 agonist by direct injection into the space between vertebrae.

Takashai teaches direct administration of a VR1 agonist such as capsaicin, a C-fiber stimulant, into rats' annulus fibrosus of disc using a microsyringe for pain that are caused by lesions in spinal disc. (see page 1, 2nd and 4th para; page 2, 2nd para). Takashai further suggests the presence of sensory C-fibers that innervates the intervertebral discs and its potential role in treating pain associated with disc lesions (see abstract, page 3, last para).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to modify Iodorola's methodology, and instead of intrathecally administering his VR1 agonist, directly administering VR1 agonists into the space between vertebrae including annulus fibrosus to treat discogenic pains of spinal column. The ordinary skill in the art would have been motivated to do such modification, because as taught by Takashai, such lesions within the spinal discs are innervated by C-fibers and one of ordinary skill in the art would have had a reasonable expectation of success in providing the pharmacological effects of VR1 agonists when administering them into vertebrae space.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh whose telephone number is 703-306-5400. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, PhD can be reached on 703-308-1877. The

fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 7-3-308-1123.

Shahnam Sharareh, PharmD
Patent Examiner, Art Unit 1617